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Anaphylactic Shock of the Lungs Triggered by Microaspiration of Cow's Milk: A Form of Sudden Unexpected Death in Early Infancy

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Introduction

In the last two decades, the frequency of deaths in early infancy has greatly diminished. This is due to the advent of newer and more exact methods of diagnosis as well as to the introduction of antibiotics and chemotherapeutics.

However, there is still a disturbing number of cases of unexpected, sudden death in early infancy (1, 2, 7, 10, 13, 14, 18, 21, 24, 25, 26, 27, 29, 30, 31). With the help of pathologists, especially in communities with high autopsy rates, the etiology of most of these cases can be determined (30).

In early infancy unexpected, sudden death is defined as the death of an individual previously considered completely healthy and exhibiting no symptoms of illness whatsoever, or only symptoms so mild as not to warrant any consternation.

All the same there remains a certain group of cases not explicable with full certainty (24, 27). Previously many such cases were attributed to "status Thymicolymphaticus". But in the light of modern evidence this concept is hardly tenable (18). Most sudden deaths can be differentiated into death by suffocation, death by fulminating infections such as laryngitis, pneumonia, bacterial sepsis and viremia (14, 25a, 18, 27, 30) or due to an underlying,

unrecognized congenital anomaly. Autopsy findings together with bacterial and viral studies have born out the diagnosis in the majority of cases. Yet in a significant number adequate evidence for a cause has not been obtainable (21, 27).

Barrett (4) in commenting on the possible causes of sudden death in infancy thinks that "perhaps the majority are due to the inhalation of regurgitated food into the lungs". He suggests that death occurred not by obstruction of the air passages but either by an inflammatory reaction with pulmonary edema or by an anaphylactic reaction due to absorption of cow's milk proteins following inhalation of otherwise insignificant amounts of milk in a sensitized infant. Evidence to support this hypothesis was presented by *Parish* et al. (23, 24) and by *Gunther* et al. (19).

These authors demonstrate that anaphylactic shock can be produced in guinea pigs sensitized to cow's milk parenterally. This same procedure is of no consequence in the non-sensitized guinea pig. In the sensitized animal, however, the shock caused by this form of artificial aspiration results in death. Furthermore, there was a difference in the response of conscious and anaesthetized guinea pigs. Also in the anaesthetized state introduction of 1 ml of cow's milk proteins into the respiratory tract led to respiratory arrest and in many cases to death. However, there was no acute emphysema usually typical of anaphylactic shock and no acute struggle. In addition, they present evidence that sensitized guinea pigs reacted to the intratracheal administration of stomach contents from 4 expired children diagnosed as "cot death".

Therefore, evidence exists indicating that anaphylactic shock by intratracheal administration, inhalation or microaspiration of milk can be elicited *in animals*.

The term microaspiration implies aspiration of an aliquot of any antigen which would be negligible in a normal, unsensitized individual and therefore would not lead to death or symptoms of shock.

In the human no convincing evidence has so far been presented as to the justification and applicability of this concept.

It is the purpose of this communication to report a case adding evidence to the correctness of this hypothesis. Some experimental data seem to point to the possibility that death from shock due to microaspiration of milk leading to an anaphylactic reaction actually occurs in the human infant.

Case Report

Clinical findings

The 7-week-old daughter of a physician (S.N. 1225-61) had been in perfect health prior to admission.

She was being breast fed but in addition received a cow's milk preparation (honey milk) with each feeding for the past 5-6 weeks. At two occasions during this period she is said to have experienced "insignificant episodes of regurgitation."

On the night of admission after having been fed, the child was placed by her mother in the crib. Shortly thereafter, a scream was noticed. Upon entering the child's room the mother found that the infant had regurgitated and was cyanotic. At this time the father took the infant by its feet, the head hanging down and slapped its back. The infant was raced to the hospital where it arrived within 6 minutes. During this period the child remained cyanotic.

On arrival, the nurse immediately aspirated from the upper and lower airways. On examination, no heart beat was detectable. Adrenalin was immediately given intracardially. The child was intubated endotracheally, the bronchial contents aspirated and artificial respiration attempted. The bronchial contents consisted of bronchial mucous and small amounts of milk.

Extrathoracic cardiac massage was started at once. Some regurgigation occurred probably on the basis of the pressure applied to thorax and abdomen from the massage. The infant was deeply cyanotic. As a result of artificial respiration and extrathoracic heart massage, the infant's appearance became progressively rosy. The pupils were in midposition, the cornea was clear. EKG examination revealed that on two occasions there were spontaneous heartbeats, once for a series of 9 incomplete ventricular complexes. Heart massage and artificial respiration were continued for 50 minutes. A cut down was performed and noradrenalin infusion begun. In the meantime the lips again became cyanotic, the pupils wide and the cornea cloudy. A total of 4 intracardial adrenalin injections had been given. The child could not be revived.

At post-mortem examination blood and lung tissue were taken for antibody studies.

Autopsy Findings

Macroscopic findings

Atelectasis of both lungs. Hyperemia of the bronchial mucosa with narrowing of the bronchial lumen. Multiple focal haematomas of the pleura. Dilatation of the right heart. Patent foramen ovale. Edema of the liver. Passive hyperemia of the kidneys. Edema of the brain. Status after intracardiac injections, status after venesections on both lower extremities.

Microscopic findings

The liver shows a fine, diffuse fatty degeneration. Focally this fatty degeneration is more intensive. The hepatic cells are somewhat large.

Evidence for myocardial edema in the presence of narrow but unaltered musclefibers.

Massive, passive hyperemia of the kidneys. The medullary cones are strongly congested.

The lungs exibit focal bleeding and atelectases. The extensively contracted bronchi contain shed epithelial cells. Only focal inflammatory infiltrations can be detected. In the periphery are some areas with desquamation of the alveolar epithelium. Examination of a second area in proximity with the hilus again reveals extensive atelectases of the lungs and minute accumulations of round cells. In all sections studied the prominent feature is the contraction of the bronchi and bronchioli, with desquamation of epithelium. There are just a few bacteria present. There is no evidence of an aspiration (Fig. 1).

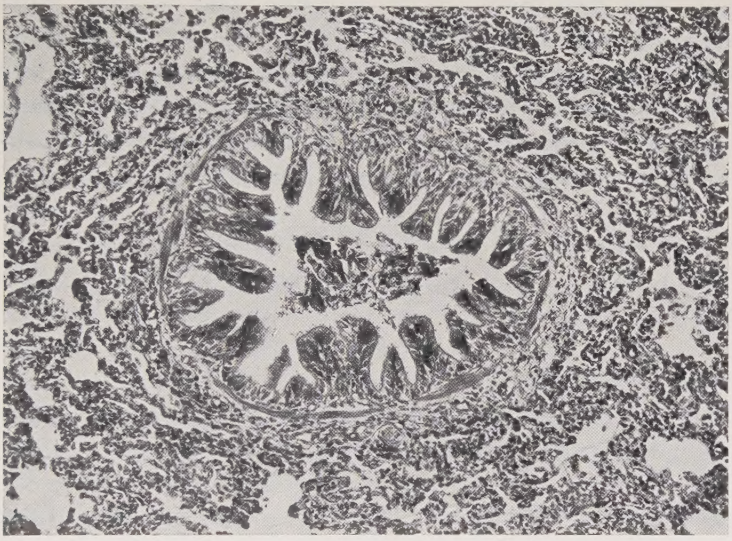

Fig. 1. Section of a major bronchus with marked contraction and desquamation of epithelial cells. No inflammatory reaction! Extensive atelectases of the lung with only minute accumulations of round cells. H.E.-stain 100 × 1.

Bronchus: Some degree of shedding of the epithelium in the absence of an inflammatory reaction.

Tonsils: An overall minimal inflammatory reaction and formation of a few plugs.

Brainstem: No inflammation. The perivascular spaces are enlarged.

Cerebral cortex: There is mild passive hyperemia with no findings for a degenerative process.

Analysis of the post-mortem findings (Prof. S. Scheidegger, Courtesy Department of Pathology, Dir. Prof. A. Werthemann):

This seven week old child died suddenly. S. N. 1225-61.

It is stated that the sudden death of the infant occurred after the evening feeding was regurgitated and possibly aspirated. The lethal outcome was of virtually immediate consequence.

Extrathoracic cardiac massage, endotracheal intubation and intracardiac injections were performed.

The macroscopic autopsy findings obtained are of uncharacteristic nature. The lungs appeared dark, hardly expanded and manifested only minimal air content.

Microscopically, however, the findings are remarkable. The lungs are extensively atelectatic and marked contractions of the bronchi and bronchioli are in evidence. The question must be raised if the extensive spastic reaction of the bronchial tree is not a result of the aspiration. Under these circumstances this phenomenon has to be considered as of allergic origin. The presence of a significant amount of aspiration, however, can be denied.

Special Laboratory Tests

The following laboratory studies were performed with the findings as listed:

Hemagglutination:

Cow's milk (as antigen) + serum from our patient: positive hemagglutination reaction with titer of 1 : 5 to 1 : 10.

Ouchterlony Plate Test:

Ouchterlony test (22) with casein and β-lactoglobulin was negative.

Complement binding reactions (K.B.R.):

Cow's milk as antigen + serum from our patient: strongly positive reaction with a titer of 1 : 656.100.

Cow's milk as antigen + washed lung extract from our patient in physiological NaCl: weakly positive.

The patient's serum was tested as an antigen against the following:

a) serum from another child positive for cow's milk anti-antibodies: negative;

b) serum from another child negative for cow's milk antibodies: negative.

The washed lung extract from our patient in physiological saline was tested as an antigen against:

a) serum from another child positive for cow's milk antibodies: positive;
b) serum from another child negative for cow's milk antibodies: negative;
c) serum from our patient: weakly positive reaction.

Discussion

We are presenting a detailed analysis of a case of sudden unexpected death in a 7 week old infant previously perfectly healthy, never having had signs of infections or other diseases. The only anamnestic information refers to two occasions of slight regurgitation.

The infant was being breast fed with the addition for 5 to 6 weeks of a cow's milk preparation.

This infant shows the typical sequence of events of a sudden unexpected death in early infancy. The anamnestic data are particularly reliable, since the father—a physician—was at home during the entire episode. From the moment the infant was heard screaming to the intervention of the father holding her in an upside-down position to free the airways hardly a minute elapsed. At this time the infant was already cyanotic and the manipulation had no visible effect. It could be determined that the time interval from the onset of symptoms to the arrival at the hospital has to be considered no more than 10 minutes.

Since the infant was actually dead on arrival, all measures taken were to no avail. It therefore must be assumed that a sudden overwhelming catastrophy led to the exitus letalis.

The autopsy was performed 13 hours after death. The results of the serologic tests were unknown to the pathologist, who independently came to the conclusion that the atelectatic lungs and markedly constricted bronchi and bronchioli must be considered as the expression of an allergic phenomenon. It appears most important *that he can definitely reject the possibility of death by gross aspiration.*

In evaluating the laboratory findings the conclusion can be reached that the child's serum contained significant amounts of antibodies against cow's milk. This is evidenced by the extremely strong complement binding reaction (5) and the positive hemagglutination reaction (6).

As another finding of significance we consider the positive reaction of the child's washed lung extract with the serum of another child whose serum was known to contain antibodies against cow's milk antigens. Conversely a negative result was obtained confronting this washed lung extract with serum from a child devoid of cow's milk antibodies. This would seem to demonstrate the presence of milk or milk antigens in the child's lungs.

However, the extract of the child's lungs also contained antibodies. This is evident from the positive KBR in matching the patient's washed lung extract with cow's milk. The actual significance of this finding is open to speculation. It can not be determined with any degree of certainty whether this presence of antibodies should be ascribed to the presence of sessile antibodies against cow's milk antigens in lung tissue and the musculature of the bronchial tree or simply to an admixture of the infant's own serum to the washed lung extract.

Conclusion

Milk allergy as a pathogenetic mechanism has been debated for many years. Some of its more subtle manifestations are beeing recognized and accepted only recently such as asthma, chronic bronchitis, intestinal anaphylactic shock and possibly even idiopathic pulmonary hemosiderosis (3, 4, 8, 9, 11, 12, 15, 16, 17, 19, 20, 23, 24, 28). Sudden unexpected death of early infancy has been added to this list only within the last years (4, 19, 23, 24). Its definite listing in this context, however, was based on experimental data obtained from animal studies only. It should be emphasized that the experiments of *Parish* et al. (23, 24) were conducted on guinea pigs whose lungs are known to act as a shock organ.

Viewed against this background our observation would seem to allow for the following cautious conclusions : sudden unexpected death in early infancy has been observed in a 7-week-old patient whose clinical history and pathological findings are

fully compatible with the concept of anaphylactic shock of the lungs. Serological data document the definite presence of antibodies to cow's milk antigens in the infant's serum. The offending cow's milk can be implicated not only on the basis of the case history and the events leading to the fatal outcome but also from the fact that in the washed lung extract its local occurrence could be demonstrated serologically. The question of the actual occurrence of sessile antibodies within the lungs can not be answered. Further studies in similar cases using lung tissue free of blood serum will eventually clarify this final question.

Summary

Case report of a 7-week-old girl brought to the hospital after sudden unexpected death subsequent to regurgitation and microaspiration of cow's milk. Postmortem and serological findings are fully compatible with the diagnosis of anaphylactic shock of the lungs in an infant sensitized to cow's milk antigens.

This case offers evidence for and support to the concept that sudden unexpected death in infancy—at least in a number of such cases—can be due to this mechanism. This concept is thus no longer based on animal experiments only. A careful study of such infants' lungs and serum with serological techniques will further clarify the mechanism of this form of an overwhelming anaphylactic reaction due to microaspiration of cow's milk and also allow for a conclusion as to its frequency among the total number of sudden unexpected deaths occurring during early infancy.

Zusammenfassung

Bericht über ein sieben Wochen altes Mädchen, das aus voller Gesundheit nach Regurgitation und Mikroaspiration von Kuhmilch völlig unerwartet starb. Die pathologischen und serologischen Befunde decken sich voll mit der Diagnose eines anaphylaktischen Schocks der Lunge bei einem kuhmilchüberempfindlichen Säugling. — Diese Beobachtung stützt die Auffassung, nach der unerwartete Todesfälle im frühen Kindesalter zumindest bei einem Teil der Fälle durch diesen Mechanismus ausgelöst sein könnten. Diese Theorie basiert somit nicht mehr ausschließlich auf tierexperimenteller Grundlage. Eine sorgfältige Untersuchung der Lungen und des Serums solcher Kinder, vor allem mit serologischer Technik, dürfte eine weitere Klärung des Mechanismus dieser Art von schwerster anaphylaktischer Reaktion infolge Mikroaspiration von Kuhmilch ermöglichen. Darüber hinaus sollte es sich zeigen, wie häufig diese Todesursache unter der gesamten Anzahl von plötzlichem unerwartetem Exitus verantwortlich zu machen ist.

Résumé

Les auteurs rapportent le cas d'une fillette de 7 semaines décédée rapidement après une régurgitation et une micro-aspiration de lait de vache. Les constatations anatomo-pathologiques et les examens sérologiques se sont révélés tout à fait compatibles avec le diagnostic de shock anaphylactique pulmonaire chez une enfant sensibilisée aux antigènes du lait de vache.

Ce cas suggère qu'un mécanisme semblable est peut-être à l'origine de certaines morts soudaines pendant le premier âge. Ce concept reposait jusqu'à présent sur des expériences chez l'animal uniquement. Il faudra encore d'autres examens anatomiques et sérologiques poussés chez de tels enfants pour rendre encore plus clair le mécanisme de cette sorte de réaction anaphylactique foudroyante. De telles études permettront aussi d'en établir la fréquence.

Resumen

Se presenta el caso de una niña de 7 semanas que se murió instantaneamente después de haber eruptado y aspirado leche de vaca en candidades muy pequeñas.

Los hallazgos de la autopsia y los resultados obtenidos con examenes serológicos estan de acuerdo con el diagnóstico del shock anafiláctico de los pulmones en un niño sensibilizado por antígenos de leche de vaca.

Este caso nos permite supponer que la muerte instantanea de niños pequeños puede ser causada por ese mecanismo por lo menos en un gran numero. Este concepto ya no esta basado en experimentos solamente con animales.

Un estudio cuidadoso con técnicas serológicas de los pulmones y del suero e esos niños nos explicara mejor el mecanismo de esa reacción tan espectacularmente fatal, debida a la microaspiración de leche de vaca, y nos permitirá llegar a la conclusión de que un gran numero de muertes instantaneas en la primer edad son debidas a esta reacción.

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Curriculum Vitae

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